AD_____

Award Number: W81XWH-12-1-0510

TITLE: Prevention of Stimulant Induced Euphoria with an Opioid Receptor Antagonist

PRINCIPAL INVESTIGATOR: Thomas Spencer, M.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

REPORT DATE: October 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2013	Annual	30September2012–29September2013

4. TITLE AND SUBTITLE
Prevention of Stimulant Induced Euphoria with an Opioid Receptor Antagonist

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-1-0510

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Thomas Spencer, M.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Massachusetts General Hospital
Boston, MA 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The protocol, sponsored by the Department of Defense, is a 6-week study examining whether Methylphenidate-induced euphoria can be attenuated by co-administration with Naltrexone In medication native young adults (age 18-30) with a euphoric response to MPH administered on the "Drug Feeling visit." In this double bind study, subjects will receive MPH and Naltrexone or a placebo to treat their ADHD symptoms over the course of the 6-week trial

15. SUBJECT TERMS- Clinical trial, methylphenidate, naltrexone, ADHD stimulant induced euphoria

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU		19b. TELEPHONE NUMBER *(include area code)*

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Table of Contents

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Section I: Introduction

The protocol, sponsored by the Department of Defense, is a 6-week study examining whether methylphenidate-induced euphoria can be attenuated by co-administration with naltrexone in medication naïve young adults (age 18-30) who exhibit a euphoric response to methylphenidate. In this double-blind study, subjects will receive methylphenidate and naltrexone or a placebo to treat their ADHD symptoms over the course of the 6-week trial.

Section II: Body

Approval from the Massachusetts General Hospital Independent Review Board (IRB) was obtained on May 30, 2013 with an approval effective date of August 10, 2012. The HRPO application was subsequently completed and submitted to the USAMRMC Office of Research Protections (ORP) on September 19, 2012. On September 25, 2012 the US Army Medical Research and Material Command (USAMRMC) informed study staff that the protocol was reviewed and found the protocol to fully comply with DoD, US Army and USAMRMC human subjects protection requirements. The study staff submitted an application to obtain an FDA IND exemption on July 11, 2011, which was received by the FDA on July 13, 2011. The IND exemption was then issued on July 18, 2011 (IND# 112804). We have also applied for and received a Certificate of Confidentiality from the NIMH, which was issued on October 23, 2012.

Unfortunately, the Principal Investigator Dr. Thomas Spencer, had a medical crisis late January/ early February 2013 and required emergency cardiac bypass surgery. We requested an unpaid extension on the study and were granted a 2 month unpaid extension on February 19, 2013. We requested an additional 2 month unpaid extension to allow for Dr. Spencer's full recovery and return to the project. Dr. Spencer has currently recovered and is back to work full time.

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program
in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Ariana Koster was hired on August 6, 2013 as the Clinical Research Coordinator for the project. She has received extensive training in recruitment procedures, subject screening, scheduling, and has been trained by the Principal Investigator to acquire in-depth knowledge of the details of the study protocol. Ariana Koster worked with Dr. Farone to develop study documents within our online database, Datstat. Ariana has worked with Dan Kaufman, the current Data Coordinator, and Laura Tarko, the departmental biostatistician, to assure that our data is accurately obtained through our electronic system and that it can be easily downloaded for data analysis. Ariana has also been trained in phlebotomy to draw the blood samples required for the study and to transfer the specimens to the Massachusetts General Hospital CORE laboratory.

Olivia Bogucki was subsequently hired as the Research Assistant for the study. She underwent training in subject recruitment, screening, data entry, and vital signs. Olivia has also been trained to preform structured diagnostic interviews (e.g., SCID, KSADS) and cognitive assessments including the 'Cognitive Screening and Neuropsychological Battery Test' as well as the 'Cambridge Neuropsychological Test Automated Battery.' Olivia has also undergone training to conduct phone screening interviews as well as gathering questionnaires and entering data.

All study staff have undergone 'Good Clinical Practice and Human Subjects Protection' training prior to involvement in the study. All study staff have also completed or updated their CITI (Collaborative Institutional Training Initiative) training and passed the CITI certification exam and are now deemed CITI certified.

Study clinicians and other research staff have been trained by the Principle Investigator on the specifics of the protocol, inclusion and exclusion criteria, and entry of rating scales into our online data system. The Principal Investigator has also trained the study clinicians to properly fill out each of the rating scales completed during study visits.

The study coordinator was assigned the task of preparing the necessary Case Report Forms (CRFs) under the supervision of the Principle investigator. To date, she has collaborated

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

with other members of study staff to create all CRFs needed for the study. The Data Manager, Study Coordinator, and Biostatistician worked to create 4D and Datstat database for the study's electronic data files. The Study Coordinator and Data Manager have worked closely during the initial phase of the study to correct any glitches and ensure that the system captures all necessary study data. On August 15, 2013, the Study Coordinator and departmental Biostatistician downloaded and cleaned the preliminary data from the study to ensure that the data can be easily analyzed upon completion of the study.

Study medication, including immediate release methylphenidate (IR MPH), long acting methylphenidate (Ritalin LA) and naltrexone HCL was ordered from the Massachusetts General Hospital Research Pharmacy. The pharmacy has created matching placebo for the IR MPH and naltrexone. Throughout the course of the study, prescriptions signed by a licensed physician on study staff are submitted to the Massachusetts General Hospital Research Pharmacy, which provides the medication required for the Drug Feeling Visits and for the randomized treatment phase of the study.

The Principal Investigator has met with all members of the DSMB to review the specifics of the protocol, inclusion and exclusion criteria, rating scales, and safety monitoring requirements for the study. Per IRB request during the 2013 Continuing Review, we changed the Chair of the DSMB from Marlene P. Freeman, MD to Dr. Joseph Gonzalez-Heydrich, who is on staff at Boston Children's Hospital, a non-Partners Healthcare affiliated institution. This change was approved on May 7, 2013 and ensures that the Chair of the DSMB is not affiliated with Massachusetts General Hospital or other Partners Healthcare networks.

A weekly team meeting is held Mondays at 1:00pm between Dr. Biederman, Dr. Spencer, the Study Coordinator, Research Assistant, and other staff necessary to review the status of the study. At the meeting, the study staff discusses new phone screens, scheduling of full in-person screens with a clinician, and recruitment initiatives. We also address issues that arise relating to already enrolled subjects, adverse events, and data management issues.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

The Study Coordinator and Research Assistant have been trained to administer an IRB-approved phone screen asking about past and current ADHD symptoms, their medical history, current and past treatment and to provide information about participating in a controlled clinical trial that involves stimulant treatment. The Study Coordinator and Research Assistant have screened potentially eligible subjects as they contact our office through our research hotline.

Those individuals who are deemed eligible by a study physician based on the phone screen, are scheduled by the Research Coordinator to meet with a clinician to conduct in-office evaluation interviews. Clinicians always obtain informed consent before preforming any study procedures. At this visit, clinicians preform a psychiatric evaluation, a physical exam, and review whether or not the individuals meet the inclusion and exclusion criteria for the study. Our first subject was consented on January 24, 2013, and we have consented 18 others since for a total of 19 enrolled subjects. 2 of these subjects have completed the entire study. The current enrollment report can be found at the end of this report in table A.

Following informed consent and an initial interview with a study physician, the Research Assistant conducts a structured interview (SCID/KSAD) and assists the Research Coordinator in obtaining vital signs, a urine pregnancy and drug test, and administration of an electrocardiogram. To date, 13 of the 19 enrolled subjects have completed these screening procedures.

To date, we have had 9 participants take part in the baseline Drug Feeling Visit to determine if they experience stimulant-induced euphoria. While we initially expected only 38% of participants experienced the desired likability response ($\geq$5 on the Drug Rating Questionnaire DRQ-S), to date 8 of the 9 subjects screened, 88.89%, have met this portion of the inclusion criteria.

Upon completing the baseline Drug Feeling Visit, we have had 7 participants move on to the randomized clinical trail for treatment with long acting methylphenidate (Ritalin LA) and double blind naltrexone. For this part of the study participants come in for weekly visits with a study physician to monitor their response to the medication, changes in their ADHD symptoms,

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

and any adverse events that arise. Medication is adjusted per the physicians' discretion and, depending on the response of the subject, may be titrated up to a maximum daily dose of 1.3mg/Kg/day. At the weekly visits, clinicians completed the AISRS and the CGI-ADHD to assess the subjects' ADHD symptoms and improvement. On the week 3 and week 6 visits, subjects repeat the protocol from the Drug Feeling Visit with double-blind doses of instant release methylphenidate (IR MPH) instead of single blind, as the rating scales obtained during this visit are used as outcome measures instead of determining subject eligibility.

For the month of June 2013, we implemented a recruitment campaign on the Massachusetts Bay Transit Authority, which consisted of 100 posters on the red line trains and 2 posters in one of the subway stations. Additionally, the Study Coordinator and Research Assistant provided our clinic's information to student health clinics at local colleges and universities. We have been in contact with student health clinics at MIT, Suffolk, Tufts, Harvard, Berklee, Emerson, and Wentworth College. On August 28, 2013 we launched a recruitment campaign on Facebook, which we continue to activate and inactivate as necessary for a steady stream of new subjects.

Section III: Key Research Accomplishments

- MGH IRB approval was obtained on May 30, 2013 with an approval effective date of August 10, 2012.
- The USAMRMC Office of Research Protections found the protocol to fully comply with DoD US Army and USAMRMC human subjects protection requirements.
- The FDA issued an IND exemption on July 11. 2011 (IND#112804).
- The NIMH issued a Certificate of Confidentiality on October 23, 2012.
- Ariana Koster was hired and trained as the Clinical Research Coordinator for the study.
- Ariana Koster has been trained in phlebotomy.
- Olivia Bogucki was hired and trained at the Research Assistant for the study.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

- Olivia Bogucki was trained to preform diagnostic interviews (e.g. KSADS, SCID) and cognitive assessments.
- All Case Report Forms (CRFs) have been created and put into our electronic data system, Datstat.
- All study staff has become CITI (Collaborative Institutional Training Initiative) certified.
- The Principal Investigator has trained research staff in the specifics of the protocol.
- Preliminary data has been downloaded and cleaned.
- Study Medication has been ordered by the MGH Research Pharmacy
- The MGH Research Pharmacy has created matching placebo for the IR MPH and naltrexone.
- The Principal Investigator has reviewed the specifics of the protocol with members of the DSMB.
- The Chair of the DSMB has been changed from Marlene P. Freeman, M.D. to Joseph Gonzolez-Heydrich, M.D.
- Weekly team meetings have been scheduled for 1:00pm on Mondays.
- We implemented a recruitment campaign on the MBTA for the month of June 2013.
- Contact information for our clinic has been provided to health clinics at local colleges and universities.
- On August 28, 2013, we launched a recruitment campaign on Facebook.
- 19 subjects have been consented and enrolled.
- 13/19 subjects have completed all screening procedures.
- 9 Participants have taken place in the baseline Drug Feeling Visit, of which 8 experienced stimulant-induced euphoria.
- 5 Participants have begun treatment in the randomized clinical trial.
- 2 Subjects have completed the entire study.

Section IV: Reportable Outcomes

To date, there are no reportable outcomes resulting from this research as the medication blind will not be broken until the end of the study to ensure the integrity of the outcome measures.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Section V: Conclusion

While stimulant medicines are documented effective treatments of ADHD across the lifecycle, persistent concerns remain about their abuse potential that greatly inhibit their therapeutic use in clinical practice. Unfortunately, untreated ADHD is associated with high levels of impairment and disability that can profoundly adversely impact the lives of those affected during and after their military service. These include difficulties performing complex and demanding cognitive tasks under time constraints as required in the military, deficits in impulsivity, distractibility and emotional regulation that could endanger the life of the affected soldier and his or her peers, deficits in the interactions with peers and superiors, emotional impulsivity that could lead to low self esteem, substance abuse, criminality and accidents [1].

ADHD also affects veterans. Upon returning to civilian life, military personnel face many hurdles in redefining their role in society and securing employment. ADHD can certainly affect the ability to negotiate this transition. One stark example of this very issue is a study of homeless veterans that found that the majority (50/80) had ADHD [2]. Thus, the safe and effective treatment of ADHD is of great importance for military personnel after active service.

In addition to causing serious problems for enlisted personnel and veterans, ADHD is also a serious problem for military families. Since ADHD is estimated to afflict up to 10% of children, a sizable number of servicemen's children may be afflicted with ADHD and suffer from its adverse impacts on the family and school. Such concerns may distract the enlisted man and interfere with the soldier's ability to perform his or her duties effectively during their absence from home. Thus, safe and effective treatment for ADHD can have a substantial, direct benefit to the families of servicemen and the piece of mind of the enlisted soldier.

Stimulants have long been used by the military for non-ADHD indications in the context of sleep loss and stress to diminish fatigue and motion sickness [3] as well as enhance alertness of pilots during lengthy flight [4, 5] as well as to enhance the abilities, marksmanship, cognitive performance and mood of soldiers [6-8].

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Yet, despite their clear and unequivocal benefits, stimulants can also be abused. For example, in a study of almost 20,000 army inductees, 12 % (2,369) reported that they had used amphetamines prior to enlistment. This number represented 38% of all cases of drug use [9]. Further surveys indicate that 10 % of military personnel abuse stimulants during active duty [10] and there is increasing concern that stimulant misuse is often from diverted prescriptions. The concern about abuse potential of stimulants is compounded by the fact that ADHD is a known risk factor for drug and alcohol abuse and dependence [11]. Hence a safe stimulant formulation free of abuse potential would allow for effective treatment of ADHD for active military personnel, their children as well as veterans without concerns about misuse, abuse and diversion.

We and others documented that the mechanism by which stimulants mediate abuse is through their effects on brain opioid receptors [12]. This insight allowed us to posit a novel pharmacological approach to help mitigate the emergence of stimulant-associated abuse by blocking opiate receptors through the use of opiate receptor antagonist naltrexone. Thus, our study could lead to the development of an abuse-free stimulant that could provide the first effective and non-addictive stimulant treatment for ADHD. Such a treatment can have profound benefits to enlisted soldiers, veterans and their families, their treating physicians and the military at large.

Section VI: References

1. Weiss, G. and L. Hechtman, *Hyperactive children grown up*, in *ADHD in children, adolescents, and adults*. 1993, Guilford Press: New York, NY.
2. Lomas, B. and P.S. Gartside, *Attention-deficit hyperactivity disorder among homeless veterans.* Psychiatr Serv, 1997. **48**(10): p. 1331-3.
3. Hoyt, R.E., et al., *Modafinil as a potential motion sickness countermeasure.* Aviat Space Environ Med, 2009. **80**(8): p. 709-15.
4. Gore, R.K., T.S. Webb, and E.D. Hermes, *Fatigue and stimulant use in military fighter aircrew during combat operations.* Aviat Space Environ Med. **81**(8): p. 719-27.
5. Caldwell, J.A. and J.L. Caldwell, *Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures.* Aviat Space Environ Med, 2005. **76**(7 Suppl): p. C39-51.
6. Caldwell, J.A., et al., *Modafinil's effects on simulator performance and mood in pilots*

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

during 37 h without sleep. Aviat Space Environ Med, 2004. **75**(9): p. 777-84.

7. McLellan, T.M., et al., *Caffeine maintains vigilance and marksmanship in simulated urban operations with sleep deprivation.* Aviat Space Environ Med, 2005. **76**(1): p. 39-45.
8. Westcott, K.J., *Modafinil, sleep deprivation, and cognitive function in military and medical settings.* Mil Med, 2005. **170**(4): p. 333-5.
9. Callan, J.P. and C.D. Patterson, *Patterns of drug abuse among military inductees.* Am J Psychiatry, 1973. **130**(3): p. 260-4.
10. Black, S., K.L. Owens, and R.P. Wolff, *Patterns of drug use: a study of 5,482 subjects.* Am J Psychiatry, 1970. **127**(4): p. 420-3.
11. Wilens, T.E., et al., *Does ADHD Predict Substance-Use Disorders? A 10-Year Follow-up Study of Young Adults With ADHD.* J Am Acad Child Adolesc Psychiatry. **50**(6): p. 543-53.
12. Zhu, J., et al., *Methylphenidate and mu opioid receptor interactions: A pharmacological target for prevention of stimulant abuse.* Neuropharmacology, 2011. **61**(1-2): p. 283-92.

Section VII: Appendices

This report does not contain appendices.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Section VIII: Supporting Data

Table A: Enrollment Report

Self-Reported Ethnicity and Gender of All Enrolled Subjects				
Ethnic Category	**Males**	**Females**	**Unknown**	**Total**
Hispanic or Latino	2	2	0	4**
Not Hispanic or Latino	5	10	0	15
Unknown (individuals not reporting ethnicity)	0	0	0	0
Totals of All Enrolled Subjects*	7	12	0	19*
***Ethnic and Racial Categories: These totals must agree.**				

Self-Reported Race and Gender of All Enrolled Subjects				
Racial Categories	**Males**	**Females**	**Unknown**	**Total**
American Indian/Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	1	0	2
White	6	10	0	16
More than one race	0	1	0	1
Unknown or not reported	0	0	0	0
Totals of All Enrolled Subjects*	7	12	0	19*
***Ethnic and Racial Categories: These totals must agree.**				

Self-Reported Race and Gender of All Enrolled Hispanic or Latino Subjects				
Racial Categories	**Males**	**Females**	**Unknown**	**Total**
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	0	0	1
White	1	1	0	2
More than one race	0	1	0	1
Unknown or not reported	0	0	0	0
Totals of Enrolled Hispanic or Latino Subjects**	2	2	0	4**
****Hispanic or Latino Ethnic and Hispanic or Latino Race Enrollment Reports: These totals must agree.**				

Ethnic and Racial Definitions for the Minimum Standard Categories Above	
Hispanic or Latino:	A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
American Indian or Alaska Native:	A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian:	A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent.
Native Hawaiian or Other Pacific Islander:	A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
Black or African American:	A person having origins in any of the black racial groups of Africa.
White:	A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry
Harvard Medical School

Table B: Adverse Events Log

Master Adverse Events Log: Prevention of Stimulant Induced Euphoria with an Opioid Receptor Antagonist

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1770901	7/29/13	Headache	Mild	Expected	Unrelated	Pharmacologic	N/A
1770401	7/29/13	Seasonal Allergies	Mild	Expected	Unrelated	Pharmacologic	N/A
1770401	8/13/13	Mild Abdominal Discomfort	Mild	Expected	Probable	None	N/A
1770401	8/3/13	Increased Energy	Mild	Expected	Probable	None	N/A
1770401	8/3/13	Agitated/Irritable	Mild	Expected	Probable	None	N/A
1770401	8/19/13	Headache	Moderate	Expected	Unrelated	None	N/A
1770401	8/29/13	Headache Pain 5/10	Moderate	Expected	Possible	None	N/A
1770401	9/6/13	Headache When sstopped coffee	Moderate	Expected	Possible	None	N/A
1770401	9/14/13	Decreased Energy. Hard to get up in AM	Moderate	Expected	Possible	None	N/A
1770701	7/16/13	Stomache discomfort due to food	Mild	Expected	Unrelated	None	N/A
1770701	8/3/13	Mild Headache in afternoon	Mild	Expected	Possible	None	N/A
1770701	8/15/13	Trouble falling asleep	Mild	Expected	Possible	None	N/A
1770701	8/15/13	Cough-Bronchitis	Moderate	Unexpected	Unrelated	None	N/A
1770701	8/23/13	Difficulty Falling Asleep	Mild	Expected	Probable	None	N/A
1770701	8/24/13	Delayed Sleep	Mild	Expected	Possible	None	N/A
1770701	8/29/13	Cheek Biting	Mild	Expected	Possible	Pharmacologic	N/A
1770701	9/5/13	Cheek Biting	Mild	Expected	Possible	None	N/A
1770501	8/19/13	Headache	Mild	Expected	Unrelated	Pharmacologic	N/A
1770601	9/17/13	Insomnia- Difficulty Falling Asleep	Severe	Expected	Definitely	Pharmacologic + Altered Dose/Changed schedule	N/A
1770601	9/17/13	Early Waking	Mild	Expected	Possible	None	N/A
1770601	9/17/13	Less hungry than usual	Mild	Expected	Probable	None	N/A
1770601	9/17/13	Shakey Feeling	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1770601	9/17/13	"Pressure"	Severe	Expected	Probable	Altered Dose/Changed Schedule	N/A
1770601	9/17/13	Just Nausia	Mild	Expected	Probable	None	N/A
1770601	9/17/13	Back Pain	Mild	Unexpected	Unrelated	None	N/A
1771001	9/17/13	More irritated than normal	Moderate	Expected	Possible	None	N/A
1771001	9/17/13	Decreased Appetite	Mild	Expected	Probable	None	N/A
1771001	9/17/13	Headache	Mild	Expected	Possible	Pharmacologic	N/A

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Subject ID	Date of AE	Description	Severity	Expected?	Related?	Changes/ Corrective Action	Date Reported to IRB
1770601	9/23/13	Decreased Appetite	Mild	Expected	Possible	None	N/A
1770601	9/23/13	Middle Insomnia (waking up before alarm	Mild	Expected	Possible	None	N/A
1770601	10/5/13	Increased Energy	Mild	Expected	Possible	None	N/A
1771001	9/24/13	Sad/Down	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1771001	9/24/13	anxious/worried	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1771001	9/24/13	Headache	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1770801	9/23/13	hospitalized for enlarged lymph nodes throughout the abdominal cavity	Severe	Unexpected	Unrelated	Terminated From Trial	9/23/13

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Table C: IRB Amendments to Date

Documentation of Ammendents Through September 30, 2013

AME #	Type	Description	Changes made to:	Date Approved
1	Approves Revised Consent Form	Changes study coordinator contact information, corrects minor formatting inconsistencies, clarifying that subjects will be taking Naltrexone (or placebo) once daily for the entire study, but will be taking SODAS-MPH twice daily for the entire study ,removing reference to "study diaries" as subjects will not complete diaries as part of this trial.	Consent Form	8/29/12
2	Study Staff	Added Ariana Koster as Research Coordinator	N/A	9/28/12
3	Protocol Revision	Approves revised Protocol Summary and Detailed Protocol decreasing the dose of naltrexone to 25 mg daily if the 50 mg dose is not well tolerated.	Detailed Protocol, Protocol Summary	11/2/12
4	Study Staff	Added: Jefferson Prince MD as a Co-Investigator. Removed: Anela Bolfek MD	N/A	11/15/12
5	Protocol and Consent Form Revision	Changing the IR-MPH dosing to single-blind on the first likability assessment day (pre-baseline) only. The IR-MPH dosing will remain double-blind at the week 3 and week 6 likability assessments.Adding handout "Likability Assessment Day Instructions;" Executing the clinical blood labs on the first likability assessment day instead of at the initial visit.	Detailed Protocol, Consent Form	11/28/12
6	Notification	Notification that the Certificate of Confidentiality CC-MH-12-184 (dated 10/23/2012) has been approved by the NIMH.	N/A	12/7/12

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

7	Protocol Revision	Increase of age range for eligible participants from 18-24 to 18-30. Subjects will be seen at a Massachusetts General Hospital outpatient site located at 55 Fruit St. WRN 705. Boston, MA 02114, instead of at 185 Alewife Brook Pkwy, Suite 2000. Cambridge, MA 02139.	Detailed Protocol, Protocol Summary, Consent Form	12/29/12
8	Study Staff	Added: Andrea Spencer MD & Mai Uchida as Co-Investigators.	N/A	1/2/13
9	Protocol Revision	Approves use of "Addiction Research Center Inventory -- Subject" form to be completed by the participant after completing the DQRS.	N/A	2/5/13
10	Study Staff	Added: Emma Issenberg as a Reg. Coordinator/mgr. Removed: Paul Hammerness MD	N/A	2/4/13
11	Study Staff	Added: Christopher Keary as a Co-Investigator	N/A	3/20/13
12	Consent Form Revision	Update the Consent Form with the Principal Investigator's current contact phone number and to reword the description of our office location (p.2) for improved clarity.	Consent Form	3/14/13
13	Study Staff	Added: Rebecca Grossman as a Research Assistant.	N/A	7/16/13
14	Advertizing	Approves posting for the MGH Clinical Trials Website and Broadcast Emails, images and text for Facebook advertising, and a Facebook Ad Landing Page (the internet webpage that will open if a potential subject clicks on a Facebook advertisement).	N/A	8/13/13
15	Study Staff	Amended to add Olivia Bogucki, Stephannie Furtak, Brittany Hughes, Tara Kenworthy, Amanda Pope, and Courtney Zulauf as research assistants, and remove Emma Issenberg and Katie McDermott from the study staff.	N/A	9/19/13

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

Table D: Minor Deviations

Minor Deviations Log
2012-P-000918 Prevention of Stimulant Induced Euphoria with an Opioid Receptor Antagonist
PI: Thomas Spencer, M.D.

Date Deviation Discovered	Date of Deviation	Description of Deviation	Corrective Action	Subject	Recorded by/Date
6/14/13	6/14/13	Blood draw not completed on Drug Feeling visit after 2 RAs attempted to locate the subjects veins.	Subject was determined to be ineligible at the visit and thus was dropped from the study.	RALSAI	Ariana Koster,
				1770201	9/17/13
8/5/13	8/5/13	At the Drug Feeling Visit, subject JOHGAG informed study staff last minute that he had to leave early and did not complete the final DRQS and ARCI.	The subject was reminded of the time commitment necessary to participate in the study.	JOHGAG	Ariana Koster
				1770401	9/17/13
8/24/13	8/24/13	Blood draw not completed on Drug Feeling visit after 2 RAs attempted to locate the subjects veins.	Under instruction of the PI, we did not pursue the blood sample and will continue without JOHGAG's blood sample from this visit	JOHGAG	Ariana Koster
				1770401	9/17/13
9/16/13	9/16/13	Subject JOHGAG refused to have his blood drawn for his week 6 visit as he did not want to have bruises on his arm.	Under instruction of the PI, we did not pursue the blood sample and will continue without JOHGAG's blood sample from this visit.	JOHGAG	Ariana Koster
				1770401	9/17/13

55 Fruit Street, YAW 6A
Boston, MA 02114
Tel: 617-726-1731
Email: tspencer@partners.org

Thomas J. Spencer, M.D.
Associate Chief, Joint Program in Pediatric Psychopharmacology

Associate Professor of Psychiatry Harvard Medical School

9/17/13	7/16/13	Subject screening visit was completed over several visits.	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	ALLGAX	Ariana Koster
				1770701	9/17/13
8/3/13	8/3/13	Blood draw not completed on Drug Feeling visit after 2 RAs attempted to locate the subjects veins.	Under instruction of the PI, we did not pursue the blood sample and will continue without JOHGAG's blood sample from this visit.	ALLGAX	Ariana Koster
				1770701	9/17/13
9/17/13	8/2/13	Subject screening visit was completed over several visits.	This policy is consistent with other studies within the department and we have submitted an amendment to	JULWAL	Ariana Koster
				1770601	9/17/13
8/24/13	8/24/13	Subject JOHGAG informed study staff that he needed to leave his week 3 visit early and therefor did not have a break between the morning and	Study staff re-emphasized the importance of being present for the full study visits and asked JOHGAG to confirm that he will be able to stay for the full study	JOHGAG	Ariana Koster
				1770401	9/17/13